UNITED STATES DEPARTMENT OF COMMERCE United States Patent and Trademark Office Address: COMMISSIONER FOR PATENTS P.O. Box 1450 Alexandria, Virginia 22313-1450 www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,950	06/08/2005	Terence Tai-Li Hwa	US3087 (111845-0057)	1513
	537,950 06/08/2005 Terence Tai-Li Hwa US3087 (111845-06 89 7590 08/06/2009 COCOPIO, CORY, HARGREAVES & SAVITCH LLP 0 B STREET ITTE 2100 AN DIEGO, CA 92101 ART UNIT 1631	EXAM	XAMINER	
530 B STREET			NEGIN, RUSSELL SCOTT	
SAN DIEGO, CA 92101		ART UNIT	PAPER NUMBER	
			1631	
			NOTIFICATION DATE	DELIVERY MODE
			08/06/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@procopio.com PTONotifications@procopio.com

	Application No.	Applicant(s)				
	10/537,950	HWA ET AL.				
Office Action Summary	Examiner	Art Unit				
	RUSSELL S. NEGIN	1631				
The MAILING DATE of this communication app Period for Reply	ears on the cover sheet with the c	orrespondence address				
A SHORTENED STATUTORY PERIOD FOR REPLY WHICHEVER IS LONGER, FROM THE MAILING DA - Extensions of time may be available under the provisions of 37 CFR 1.13 after SIX (6) MONTHS from the mailing date of this communication. - If NO period for reply is specified above, the maximum statutory period w - Failure to reply within the set or extended period for reply will, by statute, Any reply received by the Office later than three months after the mailing earned patent term adjustment. See 37 CFR 1.704(b).	ATE OF THIS COMMUNICATION 36(a). In no event, however, may a reply be time will apply and will expire SIX (6) MONTHS from cause the application to become ABANDONE	lely filed the mailing date of this communication. (35 U.S.C. § 133).				
Status						
1)⊠ Responsive to communication(s) filed on <u>26 Ma</u>	av 2009.					
·= · · · · · · · · · · · · · · · · · ·	action is non-final.					
<i>,</i> —	<i>,</i> —					
closed in accordance with the practice under E						
Disposition of Claims						
4)⊠ Claim(s) <u>1-31</u> is/are pending in the application.						
• • • • • • • • • • • • • • • • • • • •	4a) Of the above claim(s) <u>25-27</u> is/are withdrawn from consideration.					
5) Claim(s) is/are allowed.						
6)⊠ Claim(s) <u>1-24 and 28-31</u> is/are rejected.						
7) Claim(s) is/are objected to.						
8) Claim(s) <u>25-27</u> are subject to restriction and/or	election requirement.					
Application Papers	·					
9)☐ The specification is objected to by the Examiner.						
9)☐ The specification is objected to by the Examiner. 10)☐ The drawing(s) filed on is/are: a)☐ accepted or b)☐ objected to by the Examiner.						
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).						
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d). 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.						
Priority under 35 U.S.C. § 119	animer. Note the attached office	Action of format 10-102.				
<u> </u>						
12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f). a) All b) Some * c) None of: 1. Certified copies of the priority documents have been received.						
2. Certified copies of the priority documents have been received in Application No						
3. Copies of the certified copies of the priority documents have been received in this National Stage						
application from the International Bureau (PCT Rule 17.2(a)).						
* See the attached detailed Office action for a list of the certified copies not received.						
Attachment(s)						
1) Notice of References Cited (PTO-892)	4) Interview Summary					
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)	Paper No(s)/Mail Da 5) Notice of Informal P					
Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date	6) Other:	a.c, ppiloanoil				

DETAILED ACTION

Improper Request for Continued Examination

It is noted that an RCE was filed on 5/26/09 in response to the Office Action mailed 1/26/09. The Office Action Summary mailed on 1/26/09 mistakenly designated the Office Action as "final," but the Office Action itself did not state that it was final. The examiner sincerely regrets the error and resultant confusion to applicant. As prosecution on the merits was NOT closed, the RCE filed 5/26/09 was premature and the amendment filed 5/26/09 has been treated as an amendment filed after a NONfinal Office Action. Applicant is encouraged to contact the examiner with questions regarding this matter, or to contact an SLIE, Kendall Jones, at (571) 272-1592 with questions regarding possible refund of the fee paid with the RCE or possible application of the fee to a future RCE.

Election/Restrictions

Newly submitted claims 25-27 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

New claims 25-27 and claims 1-24 and 28-31 are directed to related methods. The related inventions are distinct if: (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed serve different functions. In this instance, new claims

25-27 have the step or varying a cis-regulatory sequence at the DNA binding site to select a predetermined combination of degrees of freedom selected from the group consisting of DNA binding thresholds for each transcription factor, Boltzmann weight for promoter occupancy, and mutual cooperativity factors between the transcription factors and RNA polymerase. Claims 1-24 and 28-31 do not have this step regarding degrees of freedom. Instead, claims 21-24 require a plurality of regulatory proteins governed by a plurality of different logic functions, each logic function resulting in a DIFFERENT response (which is not recited in new claims 25-27). Additionally, claims 1-20 and 28-31 require both contact interactions and long range interactions, which interactions are not recited in claims 25-27. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 25-27 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Comments

Applicants' amendments and request for reconsideration in the communication filed on 26 May 2009 are acknowledged and the amendments are entered.

Claims 1-31 are pending, and claims 1-24 and 28-31 are examined in this Office action.

Withdrawn Rejections

The rejections of claims 1, 3, 5, 7-8, 11, 13, 15, and 17-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al. in view of Wasiewicz et al., in further view of Kirch et al. [Oncogene, 1999, volume 18, pages 2728-2738, on previous 892 form] in view of Orkin [Cell, volume 63, 1990, pages 665-672] are withdrawn in view of amendments filed to the instant set of claims on 26 May 2009.

The rejections of claims 2 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al. in view of Wasiewicz et al. in view of Kirch et al. in view of Orkin, and further in view of Kirchhamer et al. [PNAS, volume 93, 1996, pages 9322-9328] are withdrawn in view of amendments filed to the instant set of claims on 26 May 2009.

The rejections of claims 4, 6, 14, and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al. in view of Wasiewicz et al. in view of Kirch et al. in view of Orkin, and further in view of Renkawitz [Trends in Genetics, 1990, volume 6, pages 192-197] are withdrawn in view of amendments filed to the instant set of claims on 26 May 2009.

The rejections of claims 9 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al. in view of Wasiewicz et al. in view of Kirch et al. in view of Orkin, and further in view of Ogawa [US Patent 5,535,382; issued 9 July 1996; filed 17 November 1993] are withdrawn in view of amendments filed to the instant set of claims on 26 May 2009.

Claim Rejections - 35 USC § 101

The following rejection is reiterated for claims 1-24 and necessitated by applicant's amendment for new claims 28-31:

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-24 and 28-31 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-24 and 28-31 are drawn to methods for combinatorially controlling the transcription of target genes in a cell.

As stated in MPEP 2106, section IV, if the claims are found to cover a judicial exception then the claims will be evaluated for providing a practical application of the judicial exception (*i.e.*, Law of Nature, Natural Phenomenon, or an Abstract Idea). This is in line with the recent decision in *In re Bilski*, 545 F.3d 943, 88 USPQ2d 1385 (Federal Circuit, 2008). In the instant case, the claims are drawn to an abstract idea and therefore must be evaluated further for providing a practical application of the judicial exception. Two of the possible ways for a practical application to result are: (1) if the claimed invention physically transforms an article or physical object to a different state or thing (a physical transformation), or (2) if the claimed invention otherwise produces a concrete, tangible, and useful result. In the instant case, a physical transformation of matter is not provided, as the instant claims merely encompass steps of *in silico* DNA manipulation. Even though claim 1 recites implementing a selected

logic function that produces a desired genetic response, and claim 11 recites this implementation step and generating the desired genetic response in the cell as output, these manipulations are interpreted as *in silico* transformations rather than physical transformation in light of the specification. The specification does not teach physical transformations in a cell or empirically, but rather the steps of the method are performed in a computer (see for example, page 27, lines 6-14). Furthermore, claim 21 only recites a single active step of selecting, which is neither a physical transformation or an *in silico* step. Therefore, none of said steps result in a physical transformation of matter such that the whole of the claim is statutory.

As such, the claims must be further evaluated for providing a practical application. The result of the claims is a practical application as the claims result in the "real-world" application of understanding molecular and DNA interactions.

As set forth above, the claim **must meet** the machine-or-transformation test in order to be eligible under 35 USC 101 as statutory subject matter (*In re Bilski*, 545 F.3d 943, 88 USPQ2d 1385 (Federal Circuit, 2008). In other words, the prohibition on patenting abstract ideas has two distinct aspects: (1) when an abstract concept has no claimed practical application, it is not patentable; (2) while an abstract concept **may have a practical application**, a claim reciting an algorithm or abstract idea can state statutory subject matter only if it is embodied in, operates on, transforms, or otherwise is tied to another class of statutory subject matter under 35 U.S.C. §101 (i.e. a machine, manufacture, or composition of matter). (*Gottschalk v. Benson*, 409 U.S. 63, 175 USPQ 673, 1972), as clarified in *In re Bilski*, 545 F.3d 943, 88 USPQ2d 1385 (Federal Circuit,

2008) the test for a method claim is whether the claimed method is (1) tied to a particular machine or apparatus <u>or</u> (2) transforms a particular article to a different state or thing.

In the instant case, the method claims are not so tied to another statutory class of invention because the **method** steps that are critical to the invention are "not tied to any **particular apparatus** or **machine**" and therefore do not meet the machine-or-transformation test as set forth in *In re Bilski* 545 F.3d 943, 88 USPQ2d 1385 (Federal Circuit, 2008).

Response to arguments:

Applicant's arguments filed 26 May 2009 have been fully considered but they are not persuasive. Applicant argues that the amended version of the instant set of claims recite a physical transformation with regard to gene expression. This argument is not persuasive because claims 1-24 and 28-31 encompass embodiments that do not require physical transformations (for instance, the instantly rejected claims could be conducted in silico). As explained in the rejection above, the specification only supports the execution of method steps in claim 1 and 11 in a computer and not empirically. Furthermore, claim 21 does not recite any active method steps that could be interpreted as either in a computer or experimental (only a selecting step is recited). In other words, there is no limitation requiring a transformation of matter to occur in any of the examined claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The following rejections are NEWLY applied and necessitated by applicant's

<u>amendments</u>:

INDEFINITENESS

Claims 1-20 and 28-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

Lines 9-13 of claim 1 recite:

which applicant regards as the invention.

...the at least one logic function is implemented by producing interactions between the two or more regulatory proteins and interactive binding of the two or more regulatory proteins at corresponding DNA binding sites...

It is unclear whether the at least one logic function is implemented by producing interactions between the two or more regulatory proteins or the interactive binding between the regulatory proteins and the DNA binding sites. Especially in the instance where there is only a singular logic function and only one implementation of a logic function is required, it is unclear as to the implementation of both sets of interactions with this single logic function. Even in the case of multiple logic functions, it is unclear as to the relationship between the implementation of the logic functions and which set of interactions to which the implementation of each logic function corresponds. For the purpose of examination, it is interpreted that a logic function produces interactions between the DNA binding sites and the regulatory proteins.

Application/Control Number: 10/537,950 Page 9

Art Unit: 1631

Line 12 of claim 1 is additionally indefinite because of the limitation "corresponding binding sites." It is unclear as to what the binding sites correspond. Furthermore, as the claim continues to recite "cis-regulatory regions," it is further unclear as to whether these cis-regulatory regions are the "corresponding" binding sites or if the "corresponding" binding sites are altogether different.

Claim 1 recites the limitation "target gene" in line 12. There is insufficient antecedent basis for this limitation in the claim. It is unclear as to which previously recited gene or gene region is the "target gene."

Line 15-18 of claim 1 and lines 13-16 of claim 11 each recite selecting cooperative or competitive binding or interactions. First, it is unclear as to what these interactions are between (i.e. the regulatory proteins themselves, or the regulatory proteins and the DNA binding sites). Second, it is unclear what is intended to perform this selection. For instance, the implementation step does not appear to result in a selection as this step merely recites the intention of producing a genetic response; furthermore, the wherein clause following this implementation step limits the implementation step but does not give limitations necessary to perform the selection. Consequently, it is not clear what recitation of the claim is intended to be limited by the selection of cooperative or competitive binding (i.e. whether this is an active method step limiting to one of the regulatory proteins, or a different intended limitation). For the purposes of examination, this phrase is interpreted as an intended result of the protein interaction and not as an active method step. Thus, any protein interaction with DNA

cis-regulatory elements which comprises cooperative binding, competitive binding, or both, is interpreted to meet this intended use limitation.

The limitation "unique gene expression that does not normally occur" in lines 4-5 of claim 11 is a relative limitation which renders the claim indefinite. The term "normally" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear as to what constitutes normal gene expression as opposed to abnormal gene expression.

Claim 11 recites the limitation "the conditions" in line 5. There is insufficient antecedent basis for this limitation in the claim. It is not clear as to the metes and bounds intended by "the conditions corresponding toinputs" as the claim does not recite any specific "inputs" to which "conditions" would correspond.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following rejection is reiterated:

35 U.S.C. 103 Rejection #1:

Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al. [US Patent 5,814,618; issued 29 September 1998; filed 7 June 1995; on IDS and corresponding WIPO search report] in view of Wasiewicz et al. [Cybernetics and Systems: An International Journal, volume 31, 2000, pages 283-315 (obtained in a version where pages are numbered consecutively starting at 1)].

Claim 21 is drawn to a method of selecting DNA binding sites in a cis-regulatory region to which one or more proteins may bind in order to control gene expression.

The patent of Bujard et al. examines methods for regulating gene expression. Specifically, Bujard et al. regulates gene expression using tetracycline-responsive fusion proteins. The abstract of Bujard et al. teaches the use of two distinct ("heterologous") polypeptides as part of a fusion protein in which the first polypeptide binds to a tet operator sequence **AND** the second polypeptide inhibits transcription in eukaryotic cells (consequently a logical function using the "AND" operator exists). The peptides bind with the nucleotide sequence at relative binding positions. Additionally, the relative binding strength between the peptides and the nucleotides is regulated to a

desired expression level through modulating the concentration of tetracycline [i.e. see Figure 8 of Bujard et al. for output corresponding to a desired level of expression that is tuned using tetracycline]. Figures 6 and 9 of Bujard et al. illustrate the cis-regulatory site arrangement within the gene.

Bujard et al. does not teach genetic computing, per se, wherein each different logic function corresponds to a different gene expression.

The article of Wasiewicz et al. studies inference based on molecular computing. Specifically, Figure 1 on page 3 of Wasiewicz et al. illustrates an analytical representation of DNA oligonucletides wherein each logic function corresponds to a different set of genes that express differently.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the controlling function in regulatory DNA sequences in Bujard et al. by use of the genetic computing methods wherein each different logic function corresponds to a different gene expression in Wasiewicz et al. wherein the motivation would have been that the genetic computing methods with distinctly expressed logic functions of Wasiewicz et al. has the advantage of identifying problems that can be solved by molecular computing more efficiently that on classical electronic machines. There would have been a reasonable expectation of success in combining the empirical study of Bujard et al. with the computational study of Wasiewicz et al. because both studies are drawn to analogous principles controlling transcription of DNA using logic functions to solve biological problems.

Response to Arguments:

Applicant's arguments filed 26 May 2009 have been fully considered but they are not persuasive.

Applicant first argues on page 10 of the Remarks that Bujard et al. teaches binding of a single fusion protein, that has TWO DISTINCT polypeptides, which is different from binding of two or more regulatory proteins as claimed. Applicant continues to argue that domains of proteins may have diverse functions, but are still part of the same protein unit. This argument is not found to be persuasive because while amended claim 21 limits the input to comprises different regulatory proteins, claim 21 recites selecting cis regulatory binding sites of DNA to which two regulatory proteins are capable of binding; no binding reaction is performed or recited. Bujard et al. teaches selection of such DNA binding sites; the fact that different sections of the fusion protein in Bujard et al. bind to different regions is evidence that the selected regions have the functions recited in the claim.

Applicant further argues on page 10 of the Remarks that Bujard et al. teaches "addition" and NOT the Boolean "AND" variable. This argument is not persuasive because Boolean "AND" variables are not recited in the instant claim.

Applicant further argues that the combination of Bujard et al. and Wasiewicz et al. lacks a clear motivation/rationale because while the study of Bujard et al. is *in vivo*, the theories of Wasiewicz et al. are only conducted *in vitro*. This argument is not persuasive because the conclusion on page 23 of Wasiewicz et al. suggests applicability of the studies to bacteria (*in vivo*).

Applicant additionally argues on pages 11-12 of the Remarks that as the claims recite "combinatorial" steps, a combination of conditions must occur to result in the desired gene expression. This argument is not persuasive because combinatorial functions are not recited in the instantly rejected claim.

The following rejection is newly applied and necessitated by amendment: 35 U.S.C. 103 Rejection #2:

Claims 1, 3-8, 11, and 13-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al. in view of Wasiewicz et al. as applied to claim 21 above, in further view of Kirch et al. [Oncogene, 1999, volume 18, pages 2728-2738, on previous 892 form] in view of Orkin [Cell, volume 63, 1990, pages 665-672] in view of Renkawitz [Trends in Genetics, 1990, volume 6, pages 192-197] in view of Cho et al. [Genes & Development, 1998, volume 12, pages 3482-3487].

Claim 1 is drawn to a method for combinatorially controlling the transcription of target genes in a cell. The method comprises identifying a plurality of logic functions, wherein each logic function combines two or more inputs to generate an output comprising a unique gene expression in the cell. The method also implements at least one selected logic function that produces a desired genetic response when a combination of specified conditions is present. This implementation comprises a plurality of inputs comprising a plurality of regulatory proteins. Then, at least one logic function is implemented by producing interactions between the regulatory proteins and

the DNA binding sites. The strength and location of the regulatory regions are adjustable by varying composition of the regulatory regions. Ultimately, a selection is made between cooperative and competitive binding to the binding sites and a selection is made between cooperative and competitive binding of the two regulatory proteins with polymerase. The interactions comprise contact and long distance interactions, which are interpreted to mean short range (i.e. covalent or ionic) and longer range interactions not based on covalent or ionic interactions.

Independent claim 11 is also drawn to combinatorial transcription control for controlling gene expression with similar limitations to independent claim 1.

The patent of Bujard et al. and study of Wasiewicz et al. make obvious the methods for regulating gene expression based on genetic computing, as discussed above. Specifically, Bujard et al. regulates gene expression using tetracycline-responsive fusion proteins. Lines 54-60 of column 2 of Bujard et al. elaborate:

In a preferred embodiment, the method involves introducing into the cell a nucleic acid molecule encoding a fusion protein which inhibits transcription, the fusion protein which inhibits transcription, the fusion protein comprising a first polypeptide which binds to a tet operator sequence, operatively linked to a heterologous second polypeptide which inhibits transcription in eukaryotic cells; and modulating the concentration of a tetracycline, or analogoue thereof, in the subject. As used herein, the term "heterologous" used in reference to the second polypeptide is intended to indicate that the second polypeptide is derived from a different protein than the first polypeptide.

Consequently, the logical function is identified as two fused polypeptides collectively regulating the tet operator sequence **AND** expression in eukaryotic cells. Furthermore, the invention of Bujard et al. implements this logic function using the two distinct, regulatory proteins. The target tet repressor/operator/inducer system of sequences is on a gene molecule as illustrated in Figures 6 and 9 of Bujard et al.; this

Application/Control Number: 10/537,950 Page 16

Art Unit: 1631

type of arrangement is "cis-regulatory." Additionally, the cited passage above indicates that the binding of the peptides to the regulatory factors are adjusted through changing the composition of this cis-regulatory region by the addition of tetracycline, which alters the binding strength and location of the peptides (i.e. at a high tetracycline concentration, binding at a particular location is inhibited). The article of Wasiewicz et al. studies inference based on molecular computing. Specifically, Figure 1 on page 3 of Wasiewicz et al. illustrates an analytical representation of DNA oligonucletides wherein each logic function corresponds to a different set of genes that express differently.

However, Bujard et al. and Wasiewicz et al. do not teach adjusting the actual composition of the nucleic acid sequence in the cis-regulatory region itself in order to adjust transcription. Additionally, Bujard et al. does not teach the role of protein-protein interactions in regulating transcription, nor does Bujard et al. teach long distance and contact interactions. Bujard et al. and Wasiewicz et al. do not teach competitive binding or selection of allosteric interactions.

The article of Kirch et al. studies that the expression of human p53 requires synergistic activation of transcription from the p53 promoter by AP-1, NF-kB, and Myc/Max. Specifically, Kirch et al. illustrates in Figure 2 on page 2730 that mutating the sequence composition at either the AP-1, NF-kB, or Myc/Max locus significantly reduces or eliminates transcription.

Bujard et al., Wasiewicz et al., and Kirch et al. do not teach the role of proteinprotein interactions in regulating transcription, nor does Bujard et al. teach long distance and contact interactions. The review of Orkin studies the regulations of genes in globins.

Specifically, the summary of the Orkin states on page 671:

We can be optimistic that further dissection of LCRs will delineate DNA sequences critical for these effects and associated proteins. The interaction of LCRs with individual genes must depend on specific protein-protein interactions, most likely involving a small, but elite, group of regulators.

Consequently, specific protein-protein interactions affect the transcription of erythroid related genes at "locus controlled regions." These contact interactions between proteins, in turn, result in long distance interactions in transcription regulation with genes more than 20 kb upstream of the LCR site [see last paragraph on page 665 of Orkin].

Bujard et al., Wasiewicz et al., Kirch et al. and Orkin do not teach competitive binding or selection of allosteric interactions.

The article of Renkawitz reviews transcriptional repression in eukaryotes.

Specifically, Figure 1A on page 193 of Renkawitz illustrates different types of cooperativity and competition as illustrated in Figures 1 through 4 (depending upon which Figure is selected). Consequently, Figures 1 through 4 of Renkawitz demonstrates a subset of the multitude of different types of logic functions representing cooperative and competitive interactions in biomolecules.

Bujard et al., Wasiewicz et al., Kirch et al., Orkin and Renkawitz do not teach competitive binding or selection of allosteric interactions with polymerases.

The article of Cho et al. studies allosteric interactions between capping enzyme subunits and RNA polymerase. The schematic of the protein is shown in Figure 1 of

Cho et al., and the effects of mutations on allosteric interactions with the polymerase are illustrated in Figures 2 and 3 of Cho et al.

Claims 3 and 13 are further limiting wherein the logic function selected comprises "AND." As highlighted above, the logical function comprises the operator "AND."

Claims 5 and 15 are further limiting wherein at least one of the interactions among the regulatory proteins comprise specific protein-protein interactions. Orkin teaches specific protein-protein interactions in the summary on page 671 of the article.

Claims 4 and 14 are further limiting wherein at least one of the interactions among the regulatory proteins comprises non-specific protein-protein interactions controlled by selecting binding locations.

Claims 6 and 16 are further limiting wherein at least some of the interactions among the regulatory proteins comprise protein-protein interactions mediated by collaborative competition between the regulatory proteins and a glue-like DNA-bound protein or protein complex.

Bujard et al., Wasiewicz et al., Kirch et al., and Orkin discuss specific proteinprotein and protein-DNA interactions. Orkin teaches distal, long-distance interactions in the paragraph bridging pages 665-666 of the review. However, Bujard et al., Wasiewicz et al., Kirch et al., and Orkin do not show non-specific interactions or competitive binding.

Specifically, Figure 1A on page 193 of Renkawitz illustrates competitive binding of trans-activating domains to DNA binding sites with generic, non-specific inhibitor proteins. The objective of this competitive binding is to further regulate transcription.

Claims 7 and 17 are further limiting wherein the interactive binding comprises tunable specific protein-DNA interactions which are tunable by selecting the binding strengths. As explained in lines 54-60 of column 2 in Bujard et al., tetracycline concentration is used to modulate the binding of the peptides in the fusion protein to the tet operator sequences. Additionally, Kirch et al. tunes transcription through mutation of the nucleic acid sequence at given locus.

Claims 8 and 18 are further limiting wherein the one or more cis-regulatory regions include long distance repression and activation schemes. These long distance interactions in transcription regulation with genes more than 20 kb upstream of the LCR site are taught in the last paragraph on page 665 of Orkin.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the method of gene regulation and computation of Bujard et al. and Wasiewicz et al. by the regulation of human p53 production in Kirch et al. wherein the motivation would have been that the control of p53 transcription via mutation plays a significant role in mitogenic stimulation and differentiation, and results in a regulation of p53 in tumors [see last paragraph of introduction].

Application/Control Number: 10/537,950 Page 20

Art Unit: 1631

It would have been further obvious to modify the regulation of genetic expression in Bujard et al., Wasiewicz et al., and Kirch et al. by use of the long-distance transcriptional regulation and, protein-protein interactions in Orkin wherein the motivation would have been that long-distance regulation of gene expression based on specific protein-protein interactions has a significant role in understanding developmentally regulated, multigene loci not specific to globins [see summary of Orkin on page 671].

It would also have been obvious to modify the transcription regulation systems of Bujard et al., Wasiewicz et al., Kirch et al., and Orkin by use of competitive inhibition with non-specific protein-DNA interactions of Renkawitz wherein the motivation would have been that competitive binding gives additional variables and controls for regulating transcription of a desired gene (i.e. see Figure 1 on page 193 of Renkawitz, the text in the caption and underneath the diagram).

It would have been further obvious to modify the transcription regulation systems of Bujard et al., Wasiewicz et al., Kirch et al., Orkin, and Renkawitz by use of allosteric interactions with polymerase as is Cho et al. because it is obvious to combine known elements in the prior art to yield a predictable result. In this instance, allosteric interactions involving polymerases are an alternate form of allosterics than allosterics involving DNA. There would have been a reasonable expectation of success in combining Cho et al. with Bujard et al., Wasiewicz et al., Kirch et al., Orkin, and Renkawitz because while polymerases are actively involved in the transcription and

translation of DNA, all of the prior art pertains analogously to cooperative and competitive interactions between DNA and proteins (i.e. polymerases).

Response to Arguments:

Applicant's arguments filed 26 May 2009 have been fully considered but they are not persuasive.

Applicant first argues on page 10 of the Remarks that Bujard et al. teaches binding of a single fusion protein, that has TWO DISTINCT polypeptides, which is different from binding of two or more regulatory proteins as claimed. Applicant continues to argue that domains of proteins may have diverse functions, but are still part of the same protein unit. Unlike claim 21, claims 1 and 11 recite two different inputs, which are limited to be regulatory proteins, but do not, in fact, limit the regulatory proteins to be two SEPARATE proteins. Consequently, the fusion protein of Bujard et al. does indeed comprise two different "inputs' (binding moieties) which are indeed different regulatory peptides.

Applicant argues that Bujard et al. do not disclose binding of two or more regulatory proteins and is unable to exert combinatorial control of gene expression necessary to construct logic functions. This argument is not found to be persuasive as the differing gene expression pertaining to different logic functions is taught in Wasiewicz et al. (i.e. see Figure 1).

Applicant further argues in the Remarks that Bujard et al. teaches "addition" and NOT the Boolean "AND" variable. This argument is not persuasive because the

function of the "AND" variable is to ADD variables or conditions to a search or function.

Applicant additionally argues in the Remarks that as the claims recite "combinatorial" steps, a combination of conditions must occur to result in the desired gene expression. Although applicant gives several examples of the meaning of "combinatorial processes" on page 11 of the Remarks, absent a limiting definition in the specification, the teachings of Bujard et al. are also interpreted to be combinatorial, as discussed above.

The following rejection is newly applied and necessitated by amendment:

35 U.S.C. 103 Rejection #3:

Claims 2 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al. in view of Wasiewicz et al. in view of Kirch et al. in view of Orkin in view of Renkawitz in view of Cho et al. as applied to claims 1, 3-8, 11, 13-18 and 21 above, and further in view of Kirchhamer et al. [PNAS, volume 93, 1996, pages 9322-9328].

Claims 2 and 12 are further limiting wherein the regions are modular.

Bujard et al., Wasiewicz et al., Kirch et al., Orkin, Renkawitz and Cho et al. make obvious a method of regulation transcription using interactions and logical operations, as discussed above.

Bujard et al., Wasiewicz et al., Kirch et al., Orkin, Renkawitz and Cho et al. do not show that each of their processes is modular.

Application/Control Number: 10/537,950 Page 23

Art Unit: 1631

Kirchhamer et al. studies modular cis-regulatory organization of developmentally expressed genes with specific examples including two genes transcribed in the sea urchin embryo.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the transcriptional regulation methods of Bujard et al., Wasiewicz et al., Kirch et al., Orkin, and Renkawitz by use of the modular cis-regulatory regions of Kirchhamer et al. wherein the motivation would have been that by understanding the subelements of the cis-regulatory systems as control modules, a more overall pattern of developmental gene expression can be assembled and understood [see last sentence of the introduction on page 9322 of Kirchhamer et al.]

Response to Arguments:

Applicant's arguments filed 26 May 2009 have been fully considered but they are not persuasive.

Applicant argues that the alleged missing limitations from Bujard et al. and Wasiewicz et al. are not taught in Kirchhamer et al. For the reasons discussed above, the combination of prior art teaches the relevant limitations of the instantly rejected claims.

The following rejection is newly applied and necessitated by amendment: 35 U.S.C. 103 Rejection #4:

Claims 9 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al. in view of Wasiewicz et al. in view of Kirch et al. in view of Orkin in view of Renkawitz in view of Cho et al. as applied to claims 1, 3-8, 11, 13-18 and 21 above, and further in view of Ogawa [US Patent 5,535,382; issued 9 July 1996; filed 17 November 1993].

Claims 9 and 19 are further limiting comprising after the step of identifying the at least one logical function:

--reducing the at least one logic function to a minimal conjunctive normal form; and

--implementing a first clause as an activation clause and all remaining clauses as repression clauses;

--wherein the relative binding strength is selected so that repression dominates activation.

Bujard et al., Wasiewicz et al., Kirch et al., Orkin, Renkawitz, and Cho et al. make obvious a method of regulation transcription using interactions and logical operations, as discussed above. Specifically, Kirch et al. in Figure 2 teaches a scheme where transcription is not repressed in only the wild type (the first out of five configurations or clauses); consequently, repression dominates in this respect.

However, Bujard et al., Wasiewicz et al., Kirch et al., Orkin, Renkawitz, and Cho et al. do not teach a logic function in minimal conjunctive normal form.

The invention of Ogawa describes ranking the results of a document retrieval system. In achieving this result, Ogawa simplifies queries to conjunctive normal form as illustrated in the equations of columns 5-6 of the patent.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the transcription regulation systems of Bujard et al., Wasiewicz et al., Kirch et al., Orkin, Renkawitz, and Cho et al. by use of the conjunctive normal form in Ogawa wherein the motivation would have been that minimal conjunctive normal form simplifies the form of the query/logical function [see equations in columns 5-6 of Ogawa]. There would have been a reasonable expectation of success in combining Bujard et al., Wasiewicz et al., Kirch et al., Orkin, Renkawitz, Cho et al. and Ogawa because the logic of the conjunctive normal form of Ogawa is generally applicable to the mathematical logical statements taught in Wasiewicz et al. for textual sequences of letter (i.e. in the instance of Wasiewicz et al., sequences if bases).

Response to Arguments:

Applicant's arguments filed 26 May 2009 have been fully considered but they are not persuasive.

Applicant argues that the alleged missing limitations from Bujard et al. and Wasiewicz et al. are not taught in Ogawa. For the reasons discussed above, the combination of prior art teaches the relevant limitations of the instantly rejected claims.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by

combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation to combine is stated above and reiterated below:

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the transcription regulation systems of Bujard et al., Wasiewicz et al., Kirch et al., Orkin, Renkawitz, and Cho et al. by use of the conjunctive normal form in Ogawa wherein the motivation would have been that minimal conjunctive normal form simplifies the form of the query/logical function [see equations in columns 5-6 of Ogawa]. There would have been a reasonable expectation of success in combining Bujard et al., Wasiewicz et al., Kirch et al., Orkin, Renkawitz, Cho et al. and Ogawa because the logic of the conjunctive normal form of Ogawa is generally applicable to the logical statements governing transcription in Bujard et al. and Kirch et al.

The following rejection is newly applied and necessitated by amendment:

35 U.S.C. 103 Rejection #5:

Claims 10 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al. in view of Wasiewicz et al. in view of Kirch et al. in view of Orkin in view of Renkawitz in view of Cho et al. in view of Ogawa as applied to claims 1, 3-9, 11, 13-19 and 21 above, and further in view of Gardner et al. [Nature, 2000, volume 403, pages 339-343]

Claims 10 and 20 are further limiting comprising after the step of identifying the at least one logical function:

--reducing the at least one logic function to a minimal disjunctive normal form;

--implementing a first clause as a repression clause and all remaining clauses as activation clauses.

Bujard et al., Wasiewicz et al., Kirch et al., Orkin, Renkawitz, Cho et al. and Ogawa make obvious a method of regulation transcription using logical interactions and logical operations, as discussed above. Specifically, Ogawa teaches a disjunctive normal form in Example 1 on columns 7-8 in order to simplify document queries.

Bujard et al., Wasiewicz et al., Kirch et al., Orkin, Renkawitz, Cho et al. and Ogawa, however, do not teach as a single repression clause with the remaining clauses being activation clauses.

The article of Gardner et al. studies construction of a genetic toggle switch in E. coli.

Specifically, Gardner et al. engineers a switch such as in Figure 3 on page 340 using the principles of Figure 1 on page 339 for the purpose of producing a generegulatory circuit. In Figure 3 of Gardner et al., there is a single repressor block and multiple activation (i.e. promoter) blocks.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the transcription regulation systems of Bujard et al., Wasiewicz et al., Kirch et al., Orkin, Renkawitz, and Cho et al. and the disjunctive normal form of Ogawa by use of the activation schemes of Gardner et al., because it is obvious to combine known elements in the prior art to yield a predictable result. In this instance, the combination of the Bujard et al., Wasiewicz et al., Kirch et al., Orkin, Renkawitz, Cho et al. and Gardner et al. yields a switch wherein activation dominates.

Application/Control Number: 10/537,950 Page 28

Art Unit: 1631

There would have been a reasonable expectation of success in combining these four studies because the switch of Gardner et al. is an alternate means of regulating gene expression to which the methods of Bujard et al., Kirch et al., and Ogawa are applicable.

Response to Arguments:

Applicant's arguments filed 10 October 2008 have been fully considered but they are not persuasive.

Applicant argues that the alleged missing limitations from Bujard et al. Wasiewicz et al.; are not taught in Gardner et al. For the reasons discussed above, the combination of Bujard et al. and Wasiewicz et al. teaches the relevant limitations.

Additionally, applicant argues that genetic switches (as in Gardner et al.) would require "many operations" to implement combinatorial control. This argument is not persuasive because as "combinatorial" is only recited in the preamble and not any method steps, the term is not interpreted to breathe life and meaning into the claims. Even assuming that a combinatorial process is required, absent a definition of combinatorial in the instant specification, a single interaction is interpreted to be combinatorial, and thus, the genetic switch of Gardner et al. is interpreted to encompass a "combinatorial" method.

The following rejection is reiterated:

35 U.S.C. 103 Rejection #6:

Application/Control Number: 10/537,950 Page 29

Art Unit: 1631

Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al. in view of Wasiewicz et al. as applied to claim 21 above, and further in view of Kirchhamer et al.

Claim 22 is further limiting wherein the control functions are modular.

Bujard et al. and Wasiewicz et al. make obvious a method of regulation transcription using interactions and logical operations, as discussed above.

Bujard et al. and Wasiewicz et al. do not show that each of their processes is modular (i.e. portable or movable).

Kirchhamer et al. studies modular cis-regulatory organization of developmentally expressed genes with specific examples including two genes transcribed in the sea urchin embryo (see page 9323, column 2, of Kirchhamer et al. for an example of modular functions).

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the transcriptional regulation and computational methods of Bujard et al. and Wasiewicz et al., by use of the modular cis-regulatory functions of Kirchhamer et al. wherein the motivation would have been that by understanding the subelements of the cis-regulatory systems as control modules, a more overall pattern of developmental gene expression can be assembled and understood [see last sentence of the introduction on page 9322 of Kirchhamer et al.]

Response to Arguments:

Applicant's arguments filed 26 May 2009 have been fully considered but they are not persuasive.

Applicant argues that the alleged missing limitations from Bujard et al. and Wasiewicz et al. are not taught in Kirchhamer et al. For the reasons discussed above, the combination of references teaches all of the limitations of the instant claim.

The following rejections are reiterated:

35 U.S.C. 103 Rejection #7:

Claims 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al. in view of Wasiewicz et al. as applied to claim 21 above, and further in view of Orkin.

Claim 23 is further limiting wherein the relative binding strengths and relative binding sites within the cis-regulatory region are selected to produce specific DNA protein interactions and non-specific glue-like protein-protein interactions. (For the purposes of examination, "non-specific glue-like" protein-protein interactions are interpreted to be protein-protein interactions.)

Claim 24 is further limiting comprising selecting the relative binding strengths and relative binding sites to permit distal activation and repression.

Bujard et al. and Wasiewicz et al. make obvious a method of regulation transcription using interactions and logical operations, as discussed above.

However, Bujard et al. and Wasiewicz et al. does not show protein-protein interactions.

The review of Orkin studies the regulations of genes in globins. Specifically, the summary of the Orkin states on page 671:

We can be optimistic that further dissection of LCRs will delineate DNA sequences critical for these effects and associated proteins. The interaction of LCRs with individual genes mist depend on specific protein-protein interactions , most likely involving a small, but elite, group of regulators.

Consequently, specific protein-protein interactions affect the transcription of erythroid related genes at "locus controlled regions."

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify method of gene regulation of Bujard et al. by use of the protein-protein interactions in Orkin wherein the motivation would have been that comprehending specific protein-protein interactions has a significant role in understanding developmentally regulated, multigene loci not specific to globins [see summary of Orkin on page 671].

Response to Arguments:

Applicant's arguments filed 26 May 2009 have been fully considered but they are not persuasive.

Applicant argues that the alleged missing limitations from Bujard et al. are not taught in Orkin. For the reasons discussed above, the combination of Bujard et al. and Wasiewicz et al. teaches the missing limitations.

The following rejection is newly applied and necessitated by amendment: 35 U.S.C. 103 Rejection #8:

Claims 28-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al. in view of Wasiewicz et al. in view of Kirch et al. in view of Orkin in view of Renkawitz in view of Cho et al. as applied to claims 1, 3-8, 11, 13-18 and 21 above, and further in view of Matthews et al. [US Patent 5,717,058; issued 10 February 1998; filed 18 February 1994].

Claim 28 is further limiting wherein the two or more regulatory proteins are different proteins expressed in cancer cells and the desired genetic response is activation of a reporter gene.

Claim 29 is further limiting wherein the two or more regulatory proteins are different proteins expressed in cancer cells and the desired genetic response is activation of a killer gene.

Bujard et al., Wasiewicz et al., Kirch et al., Orkin, Renkawitz, and Cho et al. make obvious a method of regulation transcription using interactions and logical operations, as discussed above.

Bujard et al., Wasiewicz et al., Kirch et al., Orkin, Renkawitz, and Cho et al. do not teach cancer related transcription and activation of reporter/killer genes.

The document of Matthews et al. studies peptide inhibitors of tax-dependent transcription. Specifically, Matthews et al. exemplifies the transcriptional methods for cancer in Example 5 in columns 54-55. Additionally, activation of reporter (i.e. Tax) genes and killer genes are described in column 29, lines 30-60 of Matthews et al.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the transcription regulation systems of Bujard et al., Wasiewicz et al., Kirch et al., Orkin, Renkawitz, and Cho et al. by use of the cancer system in Matthews et al. because it is obvious to combine known elements in the prior art to yield a predictable result. In this instance, the cancer-related transcriptional study of Matthews et al. is another means for conducting the transcription regulation studies of Bujard et al., Wasiewicz et al., Kirch et al., Orkin, Renkawitz, and Cho et al. There would have been a reasonable expectation of success in combining these studies because not only are they analogous in terms of transcriptional regulation, but Bujard et al., Wasiewicz et al., Kirch et al., Orkin, Renkawitz, and Cho et al. are generally applicable to the study of the affects of cancer on transcription in Matthews et al.

The following rejection is newly applied and necessitated by amendment: 35 U.S.C. 103 Rejection #9:

Claims 30-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al. in view of Wasiewicz et al. in view of Kirch et al. in view of Orkin in view of Renkawitz in view of Cho et al. as applied to claims 1, 3-8, 11, 13-18 and 21 above, and further in view of Ross et al. [Journal of Bacteriology, 1989, volume 171, pages 4009-4018].

Claim 30 is further limiting wherein the two or more regulatory proteins are different proteins expressed in cells subjected to an external chemical or biological agent and the desired genetic response is activation of a reporter gene.

Claim 31 is further limiting wherein the two or more regulatory proteins are different proteins expressed in cells of a subject having a disease or condition and the

desired genetic response to activation of a drug receptor of a drug for treatment of the disease or condition.

Bujard et al., Wasiewicz et al., Kirch et al., Orkin, Renkawitz, and Cho et al. make obvious a method of regulation transcription using interactions and logical operations, as discussed above.

Bujard et al., Wasiewicz et al., Kirch et al., Orkin, Renkawitz, and Cho et al. do not teach subjecting the regulatory proteins to external biological agents, or activation of a drug receptor for treatment.

The article of Ross et al. studies genetic analysis of transcriptional activation and repression in the Tn21 mer operon. Specifically, the abstract of Ross et al. teaches that transcription of the Tn21 mercury resistance operon is controlled by exposure of the mercury ion. Consequently, mercury ions affect activation of the mercury resistance operon (gene). In other words, introduction of mercury into the system increases the expression of a mercury resistance gene that assists in treatment of mercury poisoning.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the transcription regulation systems of Bujard et al., Wasiewicz et al., Kirch et al., Orkin, Renkawitz, and Cho et al. by use of the mercuric toxicity system in Ross et al. because it is obvious to combine known elements in the prior art to yield a predictable result. In this instance, the mercury toxin/drug study of Ross et al. is another means for conducting the transcription regulation studies of Bujard et al., Wasiewicz et al., Kirch et al., Orkin, Renkawitz, and Cho et al. There would have been a reasonable expectation of success in combining these studies

because not only are they analogous in terms of transcriptional regulation, but Bujard et al., Wasiewicz et al., Kirch et al., Orkin, Renkawitz, and Cho et al. are generally applicable to the study of the affects of mercury on transcription in Ross et al.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61

Application/Control Number: 10/537,950 Page 36

Art Unit: 1631

(November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)).

The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the

examiner should be directed to Russell Negin, whose telephone number is (571) 272-

1083. The examiner can normally be reached on Monday-Friday from 7am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

Supervisor, Marjorie Moran, Supervisory Patent Examiner, can be reached at (571)

272-0720.

Information regarding the status of the application may be obtained from the

Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only.

For more information on the PAIR system, contact the Electronic Business Center

(EBC) at 866-217-9197 (toll-free).

/RSN/

Russell S. Negin

1 August 2009

/Marjorie Moran/

Supervisory Patent Examiner, Art Unit 1631